The pathophysiology of mitochondrial disease as modeled in the mouse.

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Public Summary:

Scientific Abstract:
It is now clear that mitochondrial defects are associated with a plethora of clinical phenotypes in man and mouse. This is the result of the mitochondria's central role in energy production, reactive oxygen species (ROS) biology, and apoptosis, and because the mitochondrial genome consists of roughly 1500 genes distributed across the maternal mitochondrial DNA (mtDNA) and the Mendelian nuclear DNA (nDNA). While numerous pathogenic mutations in both mtDNA and nDNA mitochondrial genes have been identified in the past 21 years, the causal role of mitochondrial dysfunction in the common metabolic and degenerative diseases, cancer, and aging is still debated. However, the development of mice harboring mitochondrial gene mutations is permitting demonstration of the direct cause-and-effect relationship between mitochondrial dysfunction and disease. Mutations in nDNA-encoded mitochondrial genes involved in energy metabolism, antioxidant defenses, apoptosis via the mitochondrial permeability transition pore (mtPTP), mitochondrial fusion, and mtDNA biogenesis have already demonstrated the phenotypic importance of mitochondrial defects. These studies are being expanded by the recent development of procedures for introducing mtDNA mutations into the mouse. These studies are providing direct proof that mtDNA mutations are sufficient by themselves to generate major clinical phenotypes. As more different mtDNA types and mtDNA gene mutations are introduced into various mouse nDNA backgrounds, the potential functional role of mtDNA variation in permitting humans and mammals to adapt to different environments and in determining their predisposition to a wide array of diseases should be definitively demonstrated.